Amendments to the Specification:

Please replace the paragraph beginning at page 17, line 4, with the following rewritten paragraph:

A modulating agent as described herein may additionally comprise a CAR sequence for one or more different adhesion molecules (including, but not limited to, other CAMs) and/or one or more antibodies or fragments thereof that bind to such sequences. Linkers may, but need not, be used to separate such CAR sequence(s) and/or antibody sequence(s) from the HAV sequence(s) and/or each other. Such modulating agents may generally be used within methods in which it is desirable to simultaneously disrupt cell adhesion mediated by multiple adhesion molecules. As used herein, an "adhesion molecule" is any molecule that mediates cell adhesion via a receptor on the cell's surface. Adhesion molecules include members of the cadherin gene superfamily that are not classical cadherins *(e.g.,* proteins that do not contain an HAV sequence and/or one or more of the other characteristics recited above for classical cadherins), such as desmogleins (Dsg) and desmocollins (Dsc); integrins; members of the immunoglobulin supergene family, such as N-CAM; and other uncategorized transmembrane proteins, such as occludin) as well as extracellular matrix proteins such as laminin, fibronectin, collagens, vitronectin, entactin and tenascin. Preferred CAR sequences for inclusion within a modulating agent include Arg-Gly-Asp (RGD), which is bound by integrins (*see* Cardarelli et al., *J. Biol. Chem. 267*:23159-64, 1992); Tyr-Ile-Gly-Ser-Arg (YIGSR; SEQ ID NO: 12), which is bound by $\alpha 6\beta 1$ integrin; KYSFNYDGSE (SEQ ID NO: 13), which is bound by N-CAM; the N-CAM heparan sulfate-binding site IWKHKGRDVILKKDVRF (SEQ ID NO: 14), the putative Dsc CAR sequences YAT, FAT and YAS; the putative Dsg CAR sequence RAL; and/or the putative occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTPAATGLYVDQYLYHYCVVDPQ–E ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31), or derivatives thereof such as QSSGSLYGSQ (SEQ ID NO: 16) and QYLYHYCVVD (SEQ ID NO: 17).

Please replace the paragraph beginning at page 37, line 24, with the following rewritten paragraph:

For certain embodiments, as discussed below, a pharmaceutical composition may further comprise a modulator of cell adhesion that is mediated by one or more molecules other than cadherins. Such modulators may generally be prepared as described above, incorporating one or more non-cadherin CAR sequences and/or antibodies thereto in place of the cadherin CAR sequences and antibodies. Such compositions are particularly useful for situations in which it is desirable to inhibit cell adhesion mediated by multiple cell-adhesion molecules, such as other members of the cadherin gene superfamily that are not classical cadherins (*e.g.*, Dsg and Dsc); integrins; members of the immunoglobulin supergene family, such as N-CAM; and other uncategorized transmembrane proteins, such as occludin, as well as extracellular matrix proteins such as laminin, fibronectin, collagens, vitronectin, entactin and tenascin. Preferred CAR sequences for use within such a modulator include RGD, YIGSR (SEQ ID NO: 12), KYSFNYDGSE (SEQ ID NO: 13), IWKHKGRDVILKKDVRF (SEQ ID NO: 14), YAT, FAT, YAS, RAL and/or GVNPTAQSSGSLYGSQIYALCNQFYTP AATGLYVDQYLYHYCVVDPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31), or derivatives thereof such as QSSGSLYGSQ (SEQ ID NO: 16) and QYLYHYCVVD (SEQ ID NO: 17).

Please replace the paragraph beginning at page 54, line 4, with the following rewritten paragraph:

In one particularly preferred embodiment, a modulating agent is capable of disrupting cell adhesion mediated by multiple adhesion molecules. For example, a single branched modulating agent (or multiple agents linked to a single molecule or support material) may disrupt E-cadherin, N-cadherin, occludin, Dsc and Dsg mediated cell adhesion, thereby disrupting adherens junctions, tight junctions and desmosomes. Such an agent may comprise the cadherin CAR sequence, HAV, as well as the putative Dsc CAR sequences YAT, FAT, and YAS; the putative Dsg CAR sequence RAL; and the putative occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTP–AATGLYVDQYLYHYCVVDPQE ~~(SEQ ID NO:~~

~~15)~~ (SEQ ID NO: 31) or a derivative thereof such as QSSGSLYGSQ (SEQ ID NO: 16) or QYLYHYCVVD (SEQ ID NO: 17). Such agents serve as multifunctional disrupters of cell adhesion. Alternatively, a separate modulator of non-classical cadherin-mediated cell adhesion may be administered in conjunction with the modulating agent(s), either within the same pharmaceutical composition or separately. Preferred antibody modulating agents include Fab fragments directed against either the N-cadherin CAR sequence FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25) or E-cadherin CAR sequence LFSHAVSSNG-NH_2 (SEQ ID NO: 18). Fab fragments directed against the occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTPAATGLYVDQYLYHYCVVDPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31) may also be employed, either incorporated into a modulating agent or within a separate modulator that is administered concurrently.

Please replace the paragraph beginning at page 59, line 12, with the following rewritten paragraph:

The present invention also provides methods for enhancing drug delivery to the central nervous system of a mammal. The blood/brain barrier is largely impermeable to most neuroactive agents, and delivery of drugs to the brain of a mammal often requires invasive procedures. Using a modulating agent as described herein, however, delivery may be by, for example, systemic administration of a modulating agent-drug-targeting agent combination, injection of a modulating agent (alone or in combination with a drug and/or targeting agent) into the carotid artery or application of a skin patch comprising a modulating agent to the head of the patient. Certain preferred modulating agents for use within such methods are LRAHAVDING-NH_2 (SEQ ID NO: 21), LRAHAVDVNG-NH_2 (SEQ ID NO: 22), MRAHAVDING-NH_2 (SEQ ID NO: 23), HLGAHAVDINGNQVET-NH_2 (SEQ ID NO: 24), FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25), AHAVSE-NH_2 (SEQ ID NO: 27), AHAVDI-NH_2 (SEQ ID NO: 28), derivatives of such sequences (*e.g.*, N-Ac-LRAHAVDING-NH_2 (SEQ ID NO: 21), N-Ac-LRAHAVDVNG-NH_2 (SEQ ID NO: 22), N-Ac-MRAHAVDING-NH_2 (SEQ ID NO: 23), N-Ac-HLGAHAVDINGNQVET-NH_2 (SEQ ID NO: 24), N-Ac-FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25), N-Ac-AHAVSE-NH_2 (SEQ ID NO: 27), N-Ac-AHAVDI-NH_2 (SEQ ID NO: 28))

and modulating agents comprising such sequences or derivatives thereof. Also preferred are bi-functional modulating agents comprising a cadherin CAR sequence and the putative occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTPAATGLYV-DQYLYHYCVVDPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31), or derivatives or portions thereof such as QSSGSLYGSQ (SEQ ID NO: 16) and QYLYHYCVVD (SEQ ID NO: 17), preferably joined by a linker. Alternatively, a separate modulator of occludin-mediated cell adhesion may be administered in conjunction with the modulating agent(s), either within the same pharmaceutical composition or separately. Preferably, the peptide portion(s) of such modulating agents comprise 3-16 amino acids, more preferably 4-16 amino acids. Preferred antibody modulating agents include Fab fragments directed against the N-cadherin CAR sequence FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25). Fab fragments directed against the occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTPAATGLY-VDQYLYHYCVVDPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31) may also be employed, either incorporated into the modulating agent or administered concurrently as a separate modulator. In general, the amount of modulating agent administered varies with the method of administration and the nature of the condition to be treated or prevented, but typically varies as described above. Transfer of the drug to the central nervous system may be evaluated by appropriate means that will be apparent to those of ordinary skill in the art, such as magnetic resonance imaging (MRI) or PET scan (positron emitted tomography).

Please replace the paragraph beginning at page 69, line 3, with the following rewritten paragraph:

In one particularly preferred embodiment, a modulating agent is further capable of disrupting cell adhesion mediated by multiple adhesion molecules. Such an agent may comprise the cadherin CAR sequence, HAV, as well as and RGD sequence and/or the putative occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTP-AATGLYVDQYLYHYCVVDPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31) or a derivative thereof such as QSSGSLYGSQ (SEQ ID NO: 16) or QYLYHYCVVD (SEQ ID NO: 17). Alternatively, a separate modulator of non-classical cadherin-mediated cell adhesion may be administered in conjunction with the

modulating agent(s), either within the same pharmaceutical composition or separately. Preferred antibody modulating agents include Fab fragments directed against either the N-cadherin CAR sequence FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25) or E-cadherin CAR sequence LFSHAVSSNG-NH_2 (SEQ ID NO: 18). Fab fragments directed against the occludin CAR sequence GVNPTAQSSGSLYGSQIYALCNQFYTPAATGLYVDQYLYHYCVV-DPQE ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 31) may also be employed, either incorporated into a modulating agent or within a separate modulator that is administered concurrently.

Please replace the paragraph beginning at page 70, line 12, with the following rewritten paragraph:

Within a further aspect, modulating agents as described herein may be used for controlled inhibition of synaptic stability, resulting in increased synaptic plasticity. Within this aspect, administration of one or more modulating agents may be advantageous for repair processes within the brain, as well as learning and memory, in which neural plasticity is a key early event in the remodeling of synapses. Cell adhesion molecules, particularly N-cadherin and E-cadherin, can function to stabilize synapses, and loss of this function is thought to be the initial step in the remodeling of the synapse that is associated with learning and memory (Doherty et al., *J. Neurobiology, 26*:437-446, 1995; Martin and Kandel, *Neuron, 17*:567-570, 1996; Fannon and Colman, *Neuron, 17*:423-434, 1996). Inhibition of cadherin function by administration of one or more modulating agents that inhibit cadherin function may stimulate learning and memory. Preferred modulating agents for use within such methods include those that disrupt E-cadherin and/or N-cadherin mediated cell adhesion, such as LRAHAVDING-NH_2 (SEQ ID NO: 21), LRAHAVDVNG-NH_2 (SEQ ID NO: 22), MRAHAVDING-NH_2 (SEQ ID NO: 23), HLGAHAVDINGNQVET-NH_2 (SEQ ID NO: 24), FHLRAHAVDINGNQV-NH_2 (SEQ ID NO: 25), LYSHAVSSNG-NH_2 (SEQ ID NO: 18), AHAVSE-NH_2 (SEQ ID NO: 27), AHAVDI-NH_2 (SEQ ID NO: 28), SHAVSS-NH_2 (SEQ ID NO: 29), LFSHAVSSNG-NH_2 (SEQ ID NO: 19), derivatives of such sequences (*e.g.*, N-Ac-LRAHAVDING-NH_2 (SEQ ID NO: 21), N-Ac-LRAHAVDVNG-NH_2 (SEQ ID NO: 22), N-Ac-MRAHAVDING-NH_2 (SEQ ID NO: 23), N-Ac-HLGAHAVDINGNQVET-NH_2 (SEQ ID NO: 24), N-Ac-FHLRAHAVDINGNQV-NH_2 (SEQ

ID NO: 25), N-Ac-LYSHAVSSNG-NH_2 (SEQ ID NO: 18), N-Ac-AHAVSE-NH_2 (SEQ ID NO: 27), N-Ac-AHAVDI-NH_2 (SEQ ID NO: 28), N-Ac-SHAVSS-NH_2 (SEQ ID NO: 29), N-Ac-LFSHAVSSNG-NH_2 (SEQ ID NO: 19)) and modulating agents comprising such sequences or derivatives thereof. In addition, a preferred modulating agent may comprise one or more additional CAR sequences, such as the sequence RGD, which is bound by integrins and/or the N-CAM CAR sequence KYSFNYDGSE (SEQ ID NO: 12). As noted above, such additional sequence(s) may be separated from the HAV sequence via a linker. Alternatively, a separate modulator of integrin and/or N-CAM mediated cell adhesion may be administered in conjunction with the modulating agent(s), either within the same pharmaceutical composition or separately. Preferred antibody modulating agents include Fab fragments directed against either the N-cadherin CAR sequence FHLRAHAVDINGNQV-NH_2 ~~(SEQ ID NO: 15)~~ (SEQ ID NO: 25) or E-cadherin CAR sequence LFSHAVSSNG-NH_2 (SEQ ID NO: 19). For such aspects, administration may be via encapsulation into a delivery vehicle such as a liposome, using standard techniques, and injection into, for example, the carotid artery. Alternatively, a modulating agent may be linked to a disrupter of the blood-brain barrier. In general dosages range as described above.

Please replace the paragraph beginning at page 88, line 9, with the following rewritten paragraph:

The following modulating agents were employed at concentrations of 1 mg/ml, LRAHAVDING-NH_2 (SEQ ID NO: 21), MRAHAVDING-NH_2 (SEQ ID NO: 23), and the control peptide LRAHGVDING-NH_2 ~~(SEQ ID NO: 21)~~ (SEQ ID NO: 30). The former two peptide modulating agents harbor the cadherin CAR sequence, HAV. Cadherin function was also blocked utilizing the rabbit anti-cadherin CAR sequence antiserum designated as L7 (1:20). Normal rabbit serum (NRS; Sigma, St. Louis, MO) and the goat anti-neural cell adhesion molecule (NCAM) antiserum (Santa Cruz Biotechnology Inc., Santa Cruz, CA) were also used at a dilution of 1:20 as controls.

Please delete the section of the application entitled "Sequence Listing" immediately after the section of the specification entitled "Abstract of the Disclosure" on page 125 and insert the enclosed Sequence Listing therefor.